CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040195

Trade Name : ACETAZOLAMIDE TABLETS USP

Generic Name: Acetazolamide Tablets USP

Sponsor : Taro Pharmaceuticals, USA, Inc.

Approval Date: May 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040195

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040195

APPROVAL LETTER

ANDA 40-195

MAY 28 1997

Taro Pharmaceuticals U.S.A., Inc.
Attention: Lorraine W. Sachs
U.S. Agent for: Taro Pharmaceutical Industries, Ltd.
5 Skyline Drive
Hawthorne, NY 10532

Dear Ms. Sachs:

This refers to your abbreviated new drug application dated June 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acetazolamide Tablets USP, 125 mg and 250 mg.

Reference is also made to your amendments dated September 24, 1996, and February 13 and April 25, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Acetazolamide Tablets USP, 125 mg and 250 mg are bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diamox® Tablets 125 mg and 250 mg, respectively, of Storz Ophthalmics Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

5/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

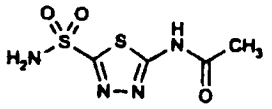
APPLICATION NUMBER 040195

FINAL PRINTED LABELING

Acetazolamide Tablets USP

DESCRIPTION

Acetazolamide, an inhibitor of the enzyme carbonic anhydrase is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for acetazolamide is *N*-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide and has the following chemical structure:



Molecular Weight: 222.25

Molecular Formula: $C_4H_6N_4O_3S_2$

Acetazolamide is available as oral tablets containing 125 mg and 250 mg of acetazolamide respectively and the following inactive ingredients: Lactose Monohydrate, Corn Starch, Gelatin, Glycerin, Purified Water, Talc, Sodium Starch Glycolate, and Magnesium Stearate.

CLINICAL PHARMACOLOGY

Acetazolamide is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion (e.g., some types of glaucoma), in the treatment of certain convulsive disorders (e.g., epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (e.g., cardiac edema).

Acetazolamide is not a mercurial diuretic. Rather, it is a nonbacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

Acetazolamide is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of aqueous humor and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain nonglaucomatous conditions. Evidence seems to indicate that acetazolamide has utility as an adjuvant in the treatment of certain dysfunctions of the central nervous system (e.g., epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of acetazolamide is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of HCO_3 ion, which carries out sodium, water, and potassium. Alkalinization of the urine and promotion of diuresis are thus effected. Alteration in ammonia metabolism occurs due to increased reabsorption of ammonia by the renal tubules as a result of urinary alkalinization.

Placebo-controlled clinical trials have shown that prophylactic administration of acetazolamide at a dose of 250 mg every eight to 12 hours (or a 500 mg controlled-release capsule once daily) before and during rapid ascent to altitude results in fewer and/or less severe symptoms (such as headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue) of acute mountain sickness (AMS). Pulmonary function (e.g., minute ventilation, expired vital capacity, and peak flow) is greater in the acetazolamide treated group, both in subjects with AMS and asymptomatic subjects. The acetazolamide treated climbers also had less difficulty in sleeping.

INDICATIONS AND USAGE

For adjunctive treatment of: edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures); chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure. Acetazolamide Tablets are also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness in climbers attempting rapid ascent and in those who are very susceptible to acute mountain sickness despite gradual ascent.

CONTRAINDICATIONS

Acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloremic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy.

Long-term administration of acetazolamide is contraindicated in patients with chronic noncongestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

WARNINGS

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitizations may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue use of this drug.

Caution is advised for patients receiving concomitant high-dose aspirin and acetazolamide, as anorexia, tachypnea, lethargy, coma and death have been reported.

PRECAUTIONS

General

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paresthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

Information for Patients

Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia and agranulocytosis. Precaution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, acetazolamide, which may precipitate or aggravate acidosis, should be used only with caution.

Gradual ascent is desirable to try to avoid acute mountain sickness. If rapid ascent is undertaken and acetazolamide tablets are used, it should be noted that such use does not obviate the need for prompt descent if severe forms of high altitude sickness occur, i.e., high altitude pulmonary edema (HAPE) or high altitude cerebral edema.

Caution is advised for patients receiving concomitant high-dose aspirin and acetazolamide, as anorexia, tachypnea, lethargy, coma and death have been reported (see WARNINGS).

Laboratory Tests

To monitor for hematologic reactions common to all sulfonamides, it is recommended that a baseline CBC and platelet count be obtained on patients prior to initiating acetazolamide tablet therapy and at regular intervals during therapy. If significant changes occur, early discontinuance and institution of appropriate therapy are important. Periodic monitoring of serum electrolytes is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of acetazolamide have not been conducted. In a bacterial mutagenicity assay, acetazolamide was not mutagenic when evaluated with and without metabolic activation.

The drug had no effect on fertility when administered in the diet to male and female rats at a daily intake of up to 4 times the recommended human dose of 1000 mg in a 50 kg individual.

Pregnancy: Teratogenic Effect: Pregnancy Category C
Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits. There are no adequate and well-controlled studies in pregnant women. Acetazolamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Because of the potential for serious adverse reaction in nursing infants from acetazolamide, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of acetazolamide in pediatric patients has not been established.

ADVERSE REACTIONS
Adverse reactions, occurring most often early in therapy, include paresthesias, particularly a "tingling" feeling in the extremities, hearing dysfunction or tinnitus, loss of appetite, taste alteration and gastrointestinal disturbances such as nausea, vomiting and diarrhea; polyuria, and occasional instances of drowsiness and confusion.

Metabolic acidosis and electrolyte imbalance may occur.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuance of the medication.

Other occasional adverse reactions include urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, photosensitivity and convulsions. Also see PRECAUTIONS: *Information for Patients* for possible reactions common to sulfonamide derivatives. Fatalities have occurred although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias (see WARNINGS).

OVERDOSAGE
No data are available regarding acetazolamide overdosage in humans as no cases of acute poisoning with this drug have been reported. Animal data suggest that acetazolamide is remarkably nontoxic. No specific antidote is known. Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state, and central nervous effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures are required to restore electrolyte and pH balance. The acidotic state can usually be corrected by the administration of bicarbonate.

Despite its high intraerythrocytic distribution and plasma protein binding properties, acetazolamide may be dialyzable. This may be particularly important in the management of acetazolamide overdosage when complicated by the presence of renal failure.

DOSAGE AND ADMINISTRATION
Glaucoma: Acetazolamide should be used as an adjunct to the usual therapy. The dosage employed in the treatment of *chronic simple (open-angle) glaucoma* ranges from 250 mg to 1 g of acetazolamide per 24 hours, usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 1 g per 24 hours does not produce an increased effect. In all cases, the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.

In treatment of secondary glaucoma and in the preoperative treatment of some cases of *acute congestive (closed-angle) glaucoma*, the preferred dosage is 250 mg every four hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every four hours depending on the individual case.

A complementary effect has been noted when acetazolamide has been used in conjunction with miotics or mydriatics as the case demanded.

Epilepsy: It is not clearly known whether the beneficial effects observed in epilepsy are due to direct inhibition of carbonic anhydrase in the central nervous system or whether they are due to the slight degree of acidosis produced by the divided dosage. The best results to date have been seen in petit mal in children. Good results, however, have been seen in patients, both children and adult, in other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk patterns, etc. The suggested total daily dose is 8 to 30 mg per kg in divided doses. Although some patients respond to a low dose, the optimum range appears to be from 375 to 1000 mg daily. However, some investigators feel that daily doses in excess of 1 g do not produce any better results than a 1 g dose. When acetazolamide tablets are given in combination with other anticonvulsants, it is suggested that the starting dose should be 250 mg once daily in addition to the existing medications. This can be increased to levels as indicated above.

The change from other medications to acetazolamide should be gradual and in accordance with usual practice in epilepsy therapy.

Congestive Heart Failure: For diuresis in congestive heart failure, the starting dose is usually 250 to 375 mg once daily in the morning (5 mg/kg). If, after an initial response, the patient fails to continue to lose edema fluid, do not increase the dose but allow for kidney recovery by skipping medication for a day. Acetazolamide tablets yield best diuretic results when given on alternate days, or for two days alternating with a day of rest.

Failures in therapy may be due to overdosage or too frequent dosage. The use of acetazolamide does not eliminate the need for other therapy such as digitalis, bed rest, and salt restriction.

Drug-Induced Edema: Recommended dosage is 250 to 375 mg of acetazolamide once a day for one or two days, alternating with a day of rest.

Acute Mountain Sickness: Dosage is 500 mg to 1000 mg daily, in divided doses. In circumstances of rapid ascent, such as in rescue or military operations, the higher dose level of 1000 mg is recommended. It is preferable to initiate dosing 24 to 48 hours before ascent and to continue for 48 hours while at high altitude, or longer as necessary to control symptoms.

Note: The dosage recommendations for glaucoma and epilepsy differ considerably from those for congestive heart failure, since the first two conditions are not dependent upon carbonic anhydrase inhibition in the kidney which requires intermittent dosage if it is to recover from the inhibitory effect of the therapeutic agent.

HOW SUPPLIED
Acetazolamide Tablets USP,
125 mg - White, round, scored in half, on one side, "T52" engraved on the other side are supplied as follows:
NDC 51672-4022-1 - Bottle of 100
250 mg - White, round, scored in quarters, on one side, "T53" engraved on the other side are supplied as follows:
NDC 51672-4023-1 - Bottle of 100
Store at Controlled Room Temperature 15-30°C (59-86°F).

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110

Distributed by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

February, 1997

Expiration Date
Lot Number

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Distributed by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

NDC 51672-4022-1

Acetazolamide Tablets USP, 125 mg

TARO **Caution:** Federal law prohibits dispensing without prescription

100 Tablets

This package not for household dispensing.
USUAL DOSAGE: For complete directions for use, see accompanying literature.

Store at Controlled Room Temperature 15-30°C (59-86°F). Dispense in well-closed containers as defined in the USP. Keep this and all medication out of the reach of children.

MAY 28 1997

Expiration Date
Lot Number

Manufactured by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Distributed by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

NDC 51672-4023-1

Acetazolamide Tablets USP, 250 mg

TARO **Caution:** Federal law prohibits dispensing without prescription

100 Tablets

This package not for household dispensing.
USUAL DOSAGE: For complete directions for use, see accompanying literature.

Store at Controlled Room Temperature 15-30°C (59-86°F). Dispense in well-closed containers as defined in the USP. Keep this and all medication out of the reach of children.

MAY 28 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040195

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
2 (TWO)

2. ANDA NUMBER
40-195

3. NAME AND ADDRESS OF APPLICANT
Taro Pharmaceuticals U.S.A., Inc.
Attention: Lorraine W. Sachs
Six Skyline Drive
Hawthorne, NY 10532

4. LEGAL BASIS for ANDA SUBMISSION
This ANDA is based upon the listed drug, Diamox® Tablets containing 125 and 250 mg of Acetazolamide manufactured by Storz Ophthalmics/Lederle Laboratories.

Taro Pharmaceutical Industries Ltd. certifies that, in its opinion and to best of its knowledge, patent information has not been submitted to the FDA. The firm also certifies that the reference listed drug is no longer entitled to a period of marketing exclusivity according to the information published in the list.

5. SUPPLEMENT(s)
None.

6. NAME OF DRUG
None.

7. NONPROPRIETARY NAME
Acetazolamide Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR
None.

9. AMENDMENTS AND OTHER DATES

Firm:	Original submission	6/21/96
	Telephone amendment	9/24/96
	Facsimile amendment	2/13/97
	Telephone amendment	4/25/97
Agency:	Telecon to firm	9/19/96
	Facsimile deficiency	1/16/97
	Telecon to firm	3/6/97
	Telecon to firm	4/21/97

10. PHARMACOLOGICAL CATEGORY

Carbonic anhydrase inhibitor.

11. HOW DISPENSED

Prescription (℞)

12. RELATED DMF(s)

Product	Holder	DMF	LOA letter

13. DOSAGE FORM

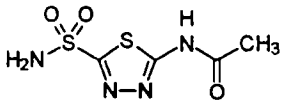
Tablet

14. POTENCY

125 mg and 250 mg

15. CHEMICAL NAME AND STRUCTURE

$C_4H_6N_4O_3S_2$. 222.25. Acetamide, *N*-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-. 59-66-5. USP 23, page 28.



16. RECORDS AND REPORTS

None.

17. COMMENTS

None.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya, Ph.D./April 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040195

BIOEQUIVALENCE REVIEW(S)

ANDA 40-195

Taro Pharmaceuticals U.S.A., Inc.
Attention: Michael Kohlbrenner
U.S. Agent for: Taro Pharmaceutical Industries, Ltd.
5 Skyline Drive
Hawthorne NY 10532

DEC 17 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acetazolamide USP, 125 mg and 250 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 12 1996

Acetazolamide
125 and 250 mg Tablets
ANDA #40-195
Reviewer: Kuldeep R. Dhariwal
Filename: 40195SDW.696

Taro Pharmaceuticals USA, Inc
5 Skyline Drive
Hawthorne, NY 10532
Submission Date:
June 21, 1996
September 24, 1996

Review of Bioequivalence Study, Dissolution Data, and Waiver Request

The firm has submitted single-dose bioequivalence study under fasting conditions and dissolution data comparing its acetazolamide 250 mg tablets with Lederle's (Storz Ophthalmics) Diamox® 250 mg tablets. The firm has also requested for waiver of *in vivo* bioequivalence study requirements for its 125 mg tablet. To support the request, the firm has submitted comparative dissolution profiles on 125 mg tablets of its product and reference listed drug Diamox®.

During the course of review, it was noticed that the firm has not submitted the individual tablet dissolution data for test and reference products. Mark Anderson called the firm on September 19, 1996 and asked the firm to submit the required data. The firm sent the data as an amendment on September 24, 1996. The reviewer received the amendment on September 25, 1996.

Introduction:

Acetazolamide is an enzyme inhibitor that acts specifically on carbonic anhydrase and is effective in the control of fluid secretion (e.g. some types of glaucoma), in the treatment of certain convulsive disorders (e.g. epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (e.g. cardiac edema).

It is N-(5-Sulfamoyl-1,3,4-thiadiazol-2yl)-acetamide. It is very slightly soluble in water and slightly soluble in alcohol. Following oral administration, acetazolamide reaches peak plasma concentration in 1 to 4 hours.

The reference listed drug is Diamox® manufactured by Lederle Laboratories for Storz Ophthalmics. It is available as oral tablets containing 125 mg and 250 mg acetazolamide; oral sustained-release capsules containing 500 mg acetazolamide; and is also available for intravenous use supplied as a sterile powder (acetazolamide sodium equivalent to 500 mg of acetazolamide) requiring reconstitution. The usual dosage is 250 to 1000 mg per day.

Bioavailability of Acetazolamide Tablets, 250 mg under Fasting Conditions:

A. Objective: The objective of this study is to determine whether Taro Pharmaceuticals U.S.A. Inc. and Lederle Laboratories (Diamox®) 250 mg acetazolamide tablets are bioequivalent under single-dose fasting conditions.

B. Study Sites and Investigators:

Clinical Site: _____

Analytical Site: _____

Medical Director: _____
Study Director: _____
Analytical Investigators: _____

Protocol #EP232 "2-Way crossover bioequivalence study of Taro Pharmaceuticals and Lederle Laboratories (Diamox®) 250 mg acetazolamide tablets in fasting volunteers" was approved by the _____

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 126, vol. 1.1.
Study Dates: Period I October 19, 1995
Period II November 2, 1995
Analysis Dates: November 7 to 24, 1995

C. Study Design:

The study was designed as a two-way, single-dose, open-label, two-treatment crossover study with a washout period of 14 days.

The subjects were housed at the _____ from approximately 10 hours prior to dosing and until after the 48 hour blood draw. The subjects were assigned as follows:

Sequence	Subject number	Period I	Period II
1	1,2,5,8,11,12,14,16,18,20,21,24	A	B
2	3,4,6,7,9,10,13,15,17,19,22,23	B	A

Subject #17 did not complete the study

A = Acetazolamide Tablets, 1x250 mg; Manufactured by Taro Pharmaceuticals; Lot #950216; Batch size: _____ Manufacture Date: July 1995; Assay: 98.8%

B = Diamox® Tablets, 1x250 mg; Lederle Laboratories; Control # 386-351; Expiry Date: Aug. 1999; Assay: 99.16%

Formulation of the test product is given in Table 1.

The subjects fasted for 10 hours prior to dosing and until 4 hours postdose. Water was permitted *ad lib.* until 2 hours before dosing and again 4 hours after dosing. Subjects were asked to engage in normal activity for the first 4 hours after drug administration, avoiding both vigorous exertion and complete rest.

D. Subject Selection:

Twenty-four Caucasian healthy male volunteers were enrolled in the study. Following inclusion and exclusion criteria were used in selecting the subjects:

- 18-45 years of age, weighing at least 60 kg, and who are within ±15% of their ideal weights (Desirable Weights of Adults- Metropolitan Life Insurance Company, 1983)
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits.

Subjects were excluded from the study based on the following criteria:

- history or presence of significant cardiovascular, hepatic, renal, CNS, hematological or gastrointestinal disease
- hypersensitivity or idiosyncratic reaction to acetazolamide or any other sulfonamides
- history or presence of suprarenal gland failure; hyperchloremic acidosis; depressed sodium and/or potassium blood serum levels
- history or presence of alcoholism or drug abuse within last year
- subjects on an abnormal diet for whatever reason during the four weeks prior to dosing
- participation in a clinical study within 4 weeks prior to the study
- donation of blood in excess of 900 mL through completion of this study in previous 20 weeks

Subjects were imposed with following restrictions:

- no medication including OTC products for 7 days prior to study
- no alcohol or caffeine-containing foods and beverages 24 hours prior to and during sample collection
- no smoking 1 hour before and 4 hours after drug administration

E. Sample Collection:

Blood samples were drawn into Vacutainers containing EDTA prior to drug administration (2x3 mL) and at the following times after dosing: 0.25,0.5,1,1.5,2,2.5,3,3.5,4,5,6,7,8,10,12,16,24,36, and 48 hours (1x3 mL). Blood samples were cooled in an ice bath, divided into two portions and stored at -12°C or lower pending assay.

F. Analytical Methods:

G. Pharmacokinetics/Statistics:

AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{½}$, and KEL were calculated. Three-way analyses of variance with sequence, subject(sequence), period, time and treatment as factors were applied. The analyses of variance included calculations of least squares means and estimated differences between the two formulations. Two one-sided t-test 90% confidence limits and ratio analysis were calculated for untransformed and log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}.

H. Results:

1. Clinical:

Twenty-four subjects entered the study. One subject withdrew prior to period 2 due to personal reasons. Subjects were monitored for clinical complaints throughout the 48 hours of confinement after drug administration.

Adverse events:

Following seven subjects experienced adverse events during the study. All events were mild in nature.

Subject #	Period	Product	Sign/Symptom
4	I	Test	Headache
6	I	Ref	Headache
7	II	Test	Left foot numbness
15	I	Ref	Nausea, sweating
20	I	Test	Tingling in hand fingers
21	I	Test	Headache
24	I	Test	Dizziness

Deviations in the study:

1. There were no protocol deviations.
2. Following deviations in scheduled phlebotomy times were reported:

Subject #	Period	Sampling time	Deviation
19	I	3.5 h	3 minutes late
22	II	0.5 h	3 minutes late
4	II	12 h	4 minutes late

Actual blood collection times were used for PK calculations.

Reassays:

Ten samples were lost during extraction and were reassayed.

2. Analytical:

3. Pharmacokinetics/Statistics:

The mean concentrations of acetazolamide at each time point after test and reference products are shown in Table 2. The time courses of acetazolamide concentration after the two products are plotted in Figures 1 and 2. The pharmacokinetic parameters are shown in Table 3. There were no statistically significant differences between the formulations for any parameter. AUC_{0-t}, AUC_{0-inf}, and C_{max} of test and reference products differed by less than 1%. The T_{max} in the test product occurred about 12 minutes earlier than in the reference product. The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Acetazolamide (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
1	315.36	380.77	315.39	380.81
10	256.48	308.92	255.16	307.59
24	271.64	333.96	270.81	333.09

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 4. The test/reference ratio for AUC_{0-t} ranged from _____ (mean 1.01), AUC_{0-inf} ranged from _____ (mean 1.01), and for C_{max} ranged from _____ with a mean of 1.01.

Table 5 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from _____ for test and _____ for reference product.

Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	99-102%	99.45-101.99%
$LNAUC_{0-inf}$	100-102%	99.86-102.15%
LNC_{max}	97-105%	96.62-104.54%

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data show significant period effect for untransformed as well as log transformed AUC_{0-t} and AUC_{0-inf}.

Subject #23 had a predose (0 hour) acetazolamide whole blood concentration of 260 ng/mL in period II. The firm attributes this to long half-life (19.03 h) of the drug in this subject. However, most subjects had half-lives of 19 hours or more but did not have detectable concentration of acetazolamide at 0 hour. This reviewer repeated statistical analysis of the data after

eliminating subject #23. The 90% confidence intervals remained within 80-125%:

$LNAUC_{0-t}$	99.89-102.3%
$LNAUC_{0-inf}$	99.99-102.34%
LNC_{max}	96.43-104.78%

In Vitro Dissolution Testing:

The dissolution testing was done by USP method using apparatus 1 (basket) at 100 rpm and 900 mL of 0.1M hydrochloric acid as medium. The drug products used in the dissolution tests were from the same lot used in the bioequivalence study. The dissolution profile of the test product is better than the reference product (Table 6).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 125 mg tablets. The comparative composition of 125 mg and 250 mg tablets is given in Table 1. The 125 mg tablet is proportionally similar in its active and inactive ingredients to the 250 mg tablet. The dissolution testing on test 125 mg tablet was done using apparatus 1 (basket) at 100 rpm and 900 ml of 0.1M hydrochloric acid as medium. The dissolution profile of the test product is slightly better than the respective strength of the reference product (Table 6).

Comments:

1. Twenty-four subjects entered the study. One subject withdrew prior to period II due to personal reasons. Seven subjects experienced adverse events during the study. All events were mild in nature.

2. There were no statistically significant differences between the two formulations for any parameter. AUC_{0-t} , AUC_{0-inf} , and C_{max} of test and reference products differed by less than 1%. The T_{max} in the test product occurred about 12 minutes earlier than in the reference product. The 90% confidence intervals for AUC_{0-t},

AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data show significant period effect for untransformed as well as log transformed AUC_{0-t} and AUC_{0-inf}.

3. The elimination half-life of the test and reference products in this study was calculated to be 19.88 and 19.53 hours respectively. The firm measured acetazolamide concentration only up to 48 hours which is about 2.5 half-lives. However, AUC_{0-t}/AUC_{0-inf} ratios for test and reference drugs in most subjects are above 0.80 (see Table 5). Therefore, though the sampling was done only up to 48 hours, it should not affect the outcome of the study.

4. The study results demonstrate that test product is bioequivalent to reference product.

5. The dissolution testing was done by USP method. The test and reference products meet the criteria: NLT_____ (Q) in 60 minutes. The dissolution results are acceptable.

6. The 125 mg tablets are proportionally similar in their active and inactive ingredients to the 250 mg tablets. The dissolution testing was done using USP method. The test and reference products meet the specifications of NLT_____ (Q) in 60 minutes. The waiver can be granted.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Taro Pharmaceuticals on its acetazolamide tablets, 250 mg, lot #950-216, comparing it to the reference product Diamox® 250 mg tablets, lot #386-351, manufactured by Lederle has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Taro Pharmaceuticals acetazolamide 250 mg tablet is bioequivalent to the reference product Diamox® 250 mg tablet manufactured by Lederle.

2. The dissolution testing conducted by Taro Pharmaceuticals on its acetazolamide 250 mg and 125 mg tablets is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1N hydrochloric acid

at 37°C using USP XXIII apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

> Not less than____ of the labeled amount of acetazolamide in the dosage form is dissolved in 60 minutes

3. The formulation for the 125 mg acetazolamide tablet is proportionally similar to the 250 mg tablet which underwent bioequivalence study. The waiver of the *in vivo* bioequivalence study requirements for Taro's 125 mg tablet is granted. The 125 mg acetazolamide tablet from Taro Pharmaceuticals is therefore deemed bioequivalent to the 125 mg Diamox® 125 mg tablet manufactured by Lederle.

4. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is approvable.

12/11/96

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 12/11/1996

Concur: _____ Date 12/12/96
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA #40195 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 092596; Final: 121196

Table 1

Comparative Quantitative Composition of Acetazolamide Tablets

Ingredients	Strength			
	125 mg		250 mg	
	mg/tablet	%w/w	mg/tablet	%w/w
Acetazolamide,USP	125.00	42.38	250.0	42.38
Lactose Monohydrate, NF				
Corn Starch, NF				
Gelatin, NF				
Glycerin, USP				
Talc, USP				
Magnesium Stearate, NF				
Sodium Starch Glycolate, NF				
Purified Water				
Total Weight	294.925	100	589.85	100

Table 2

Acetazolamide Whole Blood Concentrations (ng/mL) N = 23
Arithmetic Means and C.V. %

Time (h)	Test		Reference		Test/Ref	Signif-icance
	Mean	CV %	Mean	CV %		
0	11.0	480	0.0			NS
0.25	2714	118	1050	125	2.58	p=0.020
0.50	8299	57	5379	85	1.54	p=0.022
1.00	11173	38	8580	60	1.30	p=0.029
1.50	12144	32	10416	48	1.16	NS
2.00	12402	26	11881	36	1.04	NS
2.50	12533	24	12888	29	0.97	NS
3.00	12820	20	13452	22	0.95	NS
3.50	13277	13	13742	16	0.97	NS
4.00	13438	17	13817	14	0.97	NS
5.00	12443	17	12860	15	0.97	NS
6.00	11451	18	11781	17	0.97	p=0.039
7.00	10544	20	10773	16	0.98	NS
8.00	9837	18	9888	14	0.99	NS
10.0	8516	18	8742	16	0.97	NS
12.0	7450	18	7578	17	0.98	NS
16.0	5878	19	5982	19	0.98	NS
24.0	4437	19	4409	21	1.01	NS
36.0	2690	17	2689	21	1.00	NS
48.0	2127	19	2124	19	1.00	NS
Pharmacokinetic Parameters:						
AUC_{0-t} (ng/mLxh)	264290	14	263569	16	1.00	NS
AUC_{0-inf} (ng/mLxh)	325495	15	323640	16	1.01	NS
C_{max} (ng/mL)	15316	12	15295	15	1.00	NS
T_{max} (h)	2.48	66	2.67	47	0.93	NS
$t_{½}$ (h)	19.88	7	19.53	6	1.02	NS
Rate constant	0.0350 (h^{-1})	7	0.0356	7	0.98	NS

Table 3

Acetazolamide Whole Blood Concentrations: Pharmacokinetic Parameters: Least Squares Means ± Standard Error (n=23)

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (μg/mLxh)	264.33±1.47	263.23±1.47	1.00	
AUC_{0-inf} (μg/mLxh)	325.61±1.57	323.19±1.57	1.00	
C_{max} (μg/mL)	153.07±2.50	152.92±2.50	1.00	
T_{max} (h)	2.500±0.256	2.682±0.256	0.93	
$t_{½}$ (h)	19.887±0.19	19.519±0.19	1.02	
Rate constant (h^{-1})	0.035±0.0003	0.035±0.0003	0.98	
$LNAUC_{0-t}$	5.568±0.005	5.561±0.005	1.00	99.4-101.99%
$LNAUC_{0-inf}$	5.775±0.004	5.766±0.004	1.00	99.9-102.15%
LNC_{max}	5.024±0.016	5.018±0.016	1.00	96.6-104.54%

Table 4

Test/Reference Ratio for Pharmacokinetic Parameters in Individual Subjects

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1			
2	1			
3	2			
4	2			
5	1			
6	2			
7	2			
8	2			
9	2			
10	2			
11	1			
12	1			
13	2			
14	1			
15	2			
16	1			
18	1			
19	2			
20	1			
21	1			
22	2			
23	2			
24	1			
Mean		1.01	1.01	1.01
Range		(0.93-1.08)	(0.92-1.11)	(0.85-1.21)
CV (%)		5	5	11

Table 5

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
18		
19		
20		
21		
22		
23		
24		

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Acetazolamide Tablets
Dose Strength: 125 mg and 250 mg
ANDA No.: 40195
Firm: Taro Pharmaceuticals
Submission Date: June 21, 1996
File Name: 40195SDW.696

I. Conditions for Dissolution Testing:

USP XXIII Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium: 0.1M Hydrochloric acid Volume: 900 mL
Specifications: NLT (Q)____ in 60 minutes
Reference Drug: Diamox® Tablets (Lederle)
Assay Methodology:

USP method

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #950-217 Strength(mg) 125			Reference Product Lot #336-450 Strength(mg) 125		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.45		2.67	80.55		6.54
30	100.80		2.30	92.70		3.05
45	102.45		1.91	97.20		1.56
60	103.00		1.54	99.40		1.64

Sampling Times (Minutes)	Test Product Lot #950-216 Strength(mg) 250			Reference Product Lot #386-351 Strength(mg) 250		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86.25		2.41	60.90		19.85
30	95.00		1.98	82.10		8.78
45	99.15		1.95	90.00		4.26
60	100.10		1.25	94.85		4.47

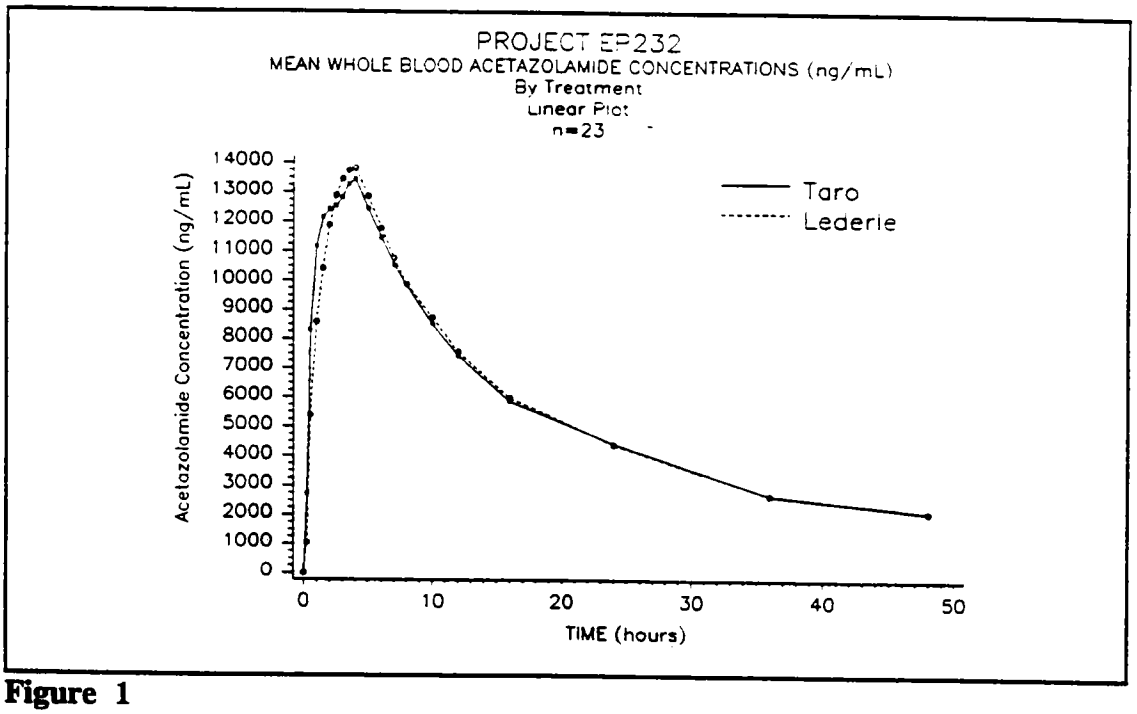


Figure 1

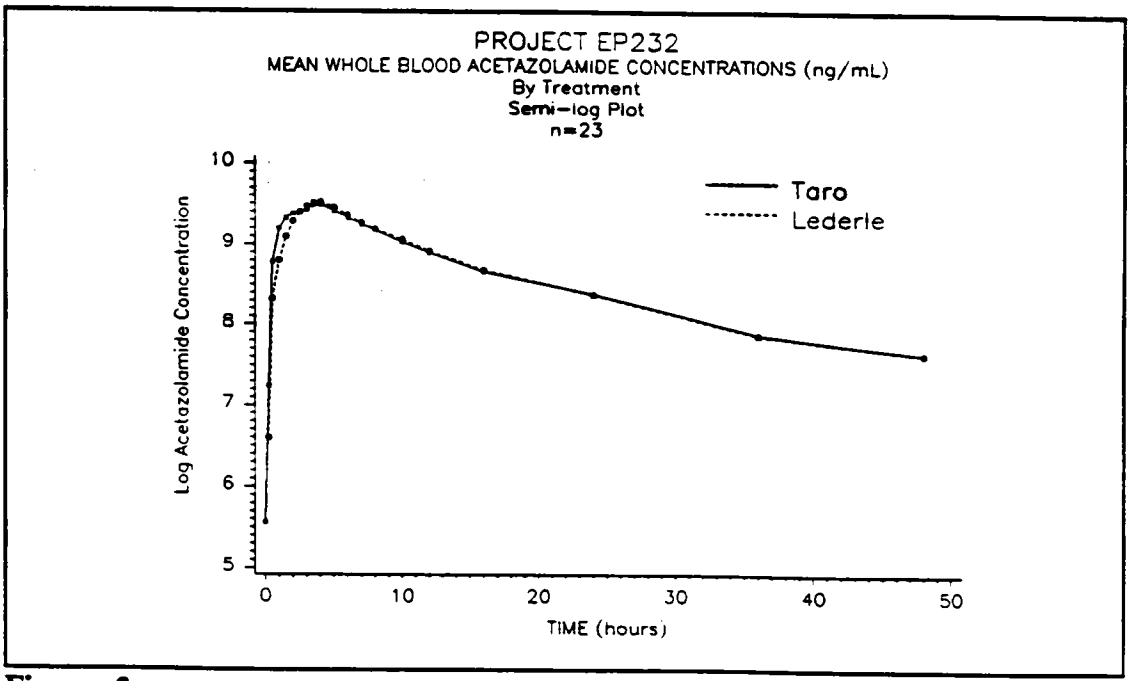


Figure 2